UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/141,220	08/27/1998	GARY A. BANNON	HS-102	9620

7590 02/09/2005

BRENDA HERSCHBACH JARRELL
CHOATE, HALL & STEWART
EXCHANGE PLACE
53 STATE STREET
BOSTON, MA 02109

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/141,220
Filing Date: August 27, 1998
Appellant(s): BANNON ET AL.

Charles E. Lyon
For Appellant

EXAMINER'S ANSWER

This is in response to the amended appeal brief filed 11/24/04.

*(1) **Real Party in Interest***

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct.

The changes are as follows:

(A) The rejection of claims 37-38, 41-43, 45-47, 49-51and 57-62 under 35 U.S.C. 102(b) as being anticipated by U. S. Pat 5,547,669 (issue 5 on page 4 of the Brief) is hereby withdrawn in view of appellant's argument that the '669 patent does not teach the step of identifying and mutating IgE binding sites. (B) Because the '669 patent is no longer available as prior art, the 103(a) rejections obvious in light of US Pat 5, 547,669 (issue 11 & 12 on page 4 of the Brief) are hereby withdrawn. Therefore, the following issues are on appeal:

(1) Claims 37-54 and 57-62 are rejected under 35 U.S.C. 112, first paragraph, for lack of written description.

(2) Claims 57-61 are rejected under 35 U.S.C. 112, first paragraph, for new matter.

(3) Claims 37-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(4) Claims 37, 39-43, 46-47, 49-51, and 57-62 are rejected under 35 U.S.C. 102(b) as being anticipated by Aki *et al* (Int Arch Allergy Immunol 103: 357-364, 1994; PTO 892).

(5) Claims 37, 40-43, 48-53, and 57-62 are rejected under 35 U.S.C. 102(a) as being anticipated by Burks *et al* (Eur. J. Biochem. 245: 334-339; 1997, PTO 1449).

(6) Claims 37, 40-43, 48-53, and 57-62 are rejected under 35 U.S.C. 102(a) as being anticipated by Stanley *et al* (Archives of Biochemistry and Biophysics 342(2): 244-253, June 1997; PTO 1449).

(7) Claims 37-38 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aki *et al* (Int Arch Allergy Immunol 103: 357-364, 1994; PTO 892) in view of WO 94/11512 publication (May 1994, PTO 892).

(8) Claims 37 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aki *et al* (Int Arch Allergy Immunol 103: 357-364, 1994; PTO 892) in view of US Pat No 6,207,646 B1 (March 2001; PTO 892).

(9) Claims 37, 48 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aki *et al* (Int Arch Allergy Immunol 103: 357-364, 1994; PTO 892) in view of Burks *et al* (Eur. J. Biochem. 245: 334-339; 1997, PTO 1449), or Stanley *et al* (Archives of Biochemistry and Biophysics 342(2): 244-253, June 1997; PTO 1449) or US Pat No. 5,449,669 (Sept 1995, PTO 892).

(7) ***Grouping of Claims***

Appellant's brief includes a statement that

(1) With regard to the written description rejection, Group A (claims 37-51 and 57-62) stand or fall together; Group B (claims 52-54 and 57-62) stand or fall together.

(2) With regard to the new matter rejection, Claims 57-61 stand or fall together.

(3) With regard to the 112 second rejection, Claim 37 stands or falls alone; claims 38-39 stand or fall together.

(4) With regard to the rejection anticipated by Aki et al, Claims 37, 39-43, 46-47, 49-51 and 57-62 stand or fall together.

(5) With regard to the rejection anticipated by Burks, Claims 37, 40-43, 48-53 and 57-62 stand or fall together.

(6) With regard to the rejection anticipated by Stanley, Claims 37, 40-43, 48-53 and 57-62 stand or fall together.

(7) With regard to the rejection obvious in light of Aki et al. and WO 94/11512, Claims 37-38 and 49 stand or fall together.

(8) With regard to the rejection obvious in light of Aki et al. and U.S. Pat. 6,207,646, Claims 37 and 44 stand or fall together.

(9) With regard to the rejection obvious in light of Aki et al. in view of Burks et al., or Stanley et al or US Pat No. 5,449,669, Claims 37, 48 and 52-54 stand or fall together.

However, with regard to issue 1, it is the examiner's position that claims 37-54 and 57-62 should stand or fall together because of the following reasons: The method of making modified *food* allergen (species) in claims 52-54 anticipates a method of making modified protein allergen (genus) of claims 37-51. Further, the dependent claims 57-62 are in both Group A and Group B. (2) With regard to issue 3, it is the examiner's position that the rejection of claims 37-39 should stand or fall together because claims 38-39 depend from claim 37.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

6,207,646	Krieg et al	03-2001
5,449,669	Metcalfe et al	09-1995
WO 94/11512	Kuo et al	05-1994

Aki et al, Int Arh Allergy Immunol 103: 357-364, 1994.

Burks *et al*, Eur. J. Biochem. 245: 334-339, April 1997.

Stanley *et al*, Archives of Biochemistry and Biophysics 342(2): 244-253, June 1997.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112 Written Description

Claims 37-54 and 57-62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey

to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of a method of making *any* modified allergen, *any* modified food allergen and *any* modified peanut allergen as set forth in claims 37-54 and 57-62. The scope of instant claims is drawn to methods of making any modified allergen, or any modified food allergen which is less reactive with IgE.

The specification discloses only a method of making modified peanut allergens selected from the group consisting of Ara h1 (SEQ ID NO: 2), Ara h2 (SEQ ID NO: 4) and Ara h3 (SEQ ID NO: 6) depicted in Figs 1-3. The amino acids that are critical for IgE binding of Ara h1, Ara h2 and Ara h3 are listed in Table 4, 5 and 6, respectively (See page 26-27). The specification also discloses that a single amino acid substitution by changing amino acid to alanine or glycine within the IgE binding epitope of Ara h1 (See page 24, line 16-18) leads to a reduced IgE binding whereas substituting alanine for arginine of Ara h1 lead to an increased IgE binding (See page 24, line 26-28). Likewise, a single amino acid within the IgE binding epitope of Ara h2 (Table 5) and Ara h3 (Table 6) would decrease IgE binding. The modified Ara h2 not only binds less serum IgE than the wild type but also binds similar amounts of IgG (See page 28, line 14-15; Fig. 4B) using serum from patients sensitive to peanut allergens. The specification further discloses that the modified Ara h2 retains the ability to stimulate T cell proliferation as measured by tritiated thymidine incorporation and the modified Ara h2 elicits a smaller wheal and flare in skin prick tests of a peanut sensitive individual (page 29).

With the exception of the specific method of making modified peanut allergen Arh 1, Ara h2 and Ara h3, there is insufficient written description about which particular one or more amino acids within the full-length sequence of all protein allergen and all food allergen to be modified for the claimed method. There is insufficient written description about the one or more amino acids such as 1-6, 1-5, 1-4, 1-3 and 1-2 amino acids in one or more of the IgE binding sites of all protein allergen such as any protein from legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, trees, weeds, mammals, birds, and natural latexes and all food allergen such as any protein obtained from legumes, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, cow milk, codfish, hazel nut, soybean and shrimp to be modified by the claimed method. Until the amino acids within the one or more IgE epitope of all protein allergen and all food allergen have been identified, the methods of making the modified allergen and food allergen are not adequately described.

Further, the specification disclosed only a method of making three species of modified food allergens from only peanut (a member of the legumes family), given the lack of a written description of any additional species of allergen from other protein allergen and food allergen as encompassed by the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).* Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 112 New Matter

Claims 57-61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The recitation of "1-6 amino acid residues" in claim 57 has no support in the specification and the claims as originally filed.

The recitation of "1-5 amino acid residues" in claim 58 has no support in the specification and the claims as originally filed.

The recitation of "1-4 amino acid residues" in claim 59 has no support in the specification and the claims as originally filed.

The recitation of "1-3 amino acid residues" in claim 60 has no support in the specification and the claims as originally filed.

The recitation of "1-2 amino acid residues" in claim 61 has no support in the specification and the claims as originally filed. Applicants have not pointed out the support for said "1-6, 1-5, 1-4, 1-3 and 1-2 amino acid residues" in at least one IgE epitope of any allergen, or any food allergen for the claimed method.

Claim Rejections - 35 USC § 112 Second paragraph

Claims 37-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "substantially the same way as the unmodified allergen" in claims 38-39 is ambiguous and indefinite because the specification does not define the term "substantially". One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

Claim Rejections - 35 USC § 102(b)

Claims 37, 39-43, 46-47, 49-51, and 57-62 are rejected under 35 U.S.C. 102(b) as being anticipated by Aki *et al* (Int Arch Allergy Immunol 103: 357-364, 1994; PTO 892).

Aki *et al* teach a method of making modified allergen such as allergen Mag1E2 from house dust mite which is less reactive with IgE (see entire document). The reference method comprises identifying one or more IgE binding sites in dust mite allergen by contacting the allergen with serum IgE from an individual or pooled serum from 8 mite-allergic patients (See page 359, column 2, page 360, column 1, in particular), modifying the allergen by mutating at least one amino acid in the center of IgE binding sites by site-directed mutagenesis such as substituting hydrophobic amino acid such as Ala, Leu, and Isolucine for neutral amino acid such as glycine or hydrophilic amino acid such as arginine and screening for IgE binding to the modified allergen using serum IgE from an individual or pooled serum from 8 mite-allergic patients (See page 361, column 1, page 360, column 1, last full paragraph, Fig. 4, in particular). The selected modified allergens such as Syn-E2 have decrease IgE binding while IgG binding is substantially the same as the unmodified allergen (see page 361, column 1, third paragraph, in particular). The reference modified allergen is a portion of the allergen which corresponds to Ser56 to Lys70 or Asp104 to Ala 115 of the unmodified dust allergen (See page 360, column 1, third paragraph, in particular). The reference modified allergen is made in a recombinant host such as bacteria (See page 358, Materials and Methods, in particular). The reference modified allergen Mag1-E2 is twelve amino acids in length and each amino acid residue was replaced with Gly by site-directed mutagenesis (See page 361, column 1, identification of the residue that participates in Binding to Specific IgE antibody, Fig 1, in particular). Aki *et al* further teach that site-directed mutagenesis in combination with IgE binding as measured by colony blot test would be effective for determining which amino acid residues in each epitope are important for the

specificity of allergic sera (See page 363, column 1, in particular). Thus, the reference teachings anticipate the claimed invention.

The filing date of the instant claims, is deemed to be the filing date of the priority application 60/073,283, 60/074,633, 60/074,624, 60/074,590 all filed Feb 13, 1998, because USSN 08/717,933 filed Sept 23, 1996 do not support the claimed limitations of "Ara h3, " in claim 48, "1-6 amino acid residues" in claim 57, 1-5 amino acid residues" in claim 58, 1-4 amino acid residues" in claim 59, 1-3 amino acid residues" in claim 60, 1-2 amino acid residues" in claim 61 in any one IgE epitope of any allergen as encompassed by the claimed method. The 08/717,933 discloses only the nucleotide molecules of the specific unmodified Ara h1 and Ara h2, the amino acid sequence of the specific modified peanut allergen Ara h1 and Ara h2 as well as antibody to Ara h1 and Ara h2 and a method of making said modified peanut allergens.

Claim Rejections - 35 USC § 102(a)

Claims 37, 40-43, 48-53, and 57-62 are rejected under 35 U.S.C. 102(a) as being anticipated by Burks *et al* (Eur. J. Biochem. 245: 334-339; 1997, PTO 1449).

Burks *et al* teach a method of making a modified allergen such as peanut allergen Ara h1which is less reactive with IgE comprising the steps of identifying one or more IgE binding sites in the reference allergen Ara h1 that bind to serum IgE from individual or pooled serum of individuals who is allergic to peanut allergen (See page 334, Materials and Methods, in particular), modifying the reference peanut allergen by mutating in the center of at least one or more amino acid in one or more IgE sites by substituting a hydrophobic amino acid (Ala) for the neutral (Gly) or hydrophilic (Ser) amino acid (See Fig 7, A25G, column 2, paragraph 1, Fig 5, in particular), screening for IgE binding of modified allergen using serum IgE from an individual or pooled serum from 15 patient with peanut-hypersensitivity (See page 337, column 2, in particular) and selecting peptide such as peptides, 1, 3, 4, and 17 which have decrease IgE binding as compared to the control unmodified wild type allergen (See Fig 6 and 7, in particular). The reference method of making modified-allergen reduces IgE binding to less than about 1% of that observed to the unmodified allergen (See Fig 4 and 5, in particular). The reference further teaches there are at least 23 different IgE binding epitopes on peanut allergen Ara 1 distributed throughout the protein and the modified allergen is a portion of said protein (See Figs 1-3, Fig 6, page 339, column 1, in particular). Burks *et al* teach it is possible to mutate the Ara h1 allergen to a protein so that it no longer binds IgE and this could be used to replace its allergenic

homologue in the peanut genome to develop a hypoallergenic peanut and for making and using hypogenic modified allergen for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph). Claims 57-61 are included in this rejection because there are 23 different IgE binding epitopes on peanut allergen Ara 1 distributed throughout the protein and anticipates the term "at least one" amino acids in at least one IgE epitope of the allergen. The reference method teaches that the modified peanut allergen is useful for developing a hypoallergenic peanut for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph). Thus, the reference teachings anticipate the claimed invention.

Claims 37, 40-43, 48-53, and 55-62 are rejected under 35 U.S.C. 102(a) as being anticipated by Stanley *et al* (Archives of Biochemistry and Biophysics 342(2): 244-253, June 1997; PTO 1449).

Stanley *et* teach a method of making a modified allergen such as peanut allergen Ara h2 which is less reactive with IgE comprising the steps of identifying one or more IgE binding sites in the reference allergen Ara h2 that bind to serum IgE from individual or pooled serum of individuals who is allergic to peanut allergen (See entire document, Fig 2, Abstract, in particular), modifying the reference peanut allergen by mutating in the center of at least one or more amino acid in one or more IgE sites by substituting a hydrophobic amino acid (Ala) for the neutral (Gly) or hydrophilic (Ser) amino acid (See Fig 5, in particular), screening for IgE binding of modified allergen using serum IgE from an individual or pooled serum from 15 patient with peanut-hypersensitivity (see caption of Fig 5, in particular), and selecting peptide such as peptides 3, 6 and 7 which have decrease IgE binding as compared to the control unmodified wild type allergen (See Figs 4 and 5, page 251 column 1, in particular). The reference method of making modified-allergen reduces IgE binding to less than about 1% of that observed to the unmodified allergen (See Fig 4 and 5, in particular). The reference further teaches there are at least ten different IgE binding epitopes on peanut allergen Ara h2 distributed throughout the protein and the modified allergen is a portion of said protein (See page 251, column 2, first full paragraph, in particular). Stanley *et al* teach it is possible to mutate the Ara h2 allergen to a protein so that it no longer binds IgE and this could be for desensitization immunotherapy (See page 252, first paragraph, in particular). Claims 57-61 are included in this rejection because there are 10 different IgE binding epitopes on peanut allergen Ara h2 distributed throughout the protein and anticipates the term "at

least one" amino acids in at least one IgE epitope of the allergen. Thus, the reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103(a)

Claims 37-38 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aki *et al* (Int Arch Allergy Immunol 103: 357-364, 1994; PTO 892) in view of WO 94/11512 publication (May 1994, PTO 892).

The teachings of Aki *et al* have been discussed supra.

The claimed invention in claim 38 differs from the teachings of the reference only in that the method further comprising screening for activation of T cells that have been cultured from an individual that is allergic to the allergen and selecting the modified allergens which activate the T cells in substantially the same way as the unmodified allergen.

The claimed invention in claim 49 differs from the teachings of the reference only in that the method wherein the modified allergen is based on a protein obtained from trees.

WO 94/11512 publication teaches a method of making modified allergen from tree such as Cryptomeria japonica major pollen allergen Cry j II by screening for IgE binding (See page 36, Example 6) and T cell activation such as T cell proliferation assays and selecting modified allergen which activate T cells equal to or greater than 2 times the background level of the background control peptide (See page 38-39, page 8, lines 9-18, in particular). WO 94/11512 publication teaches Cry j II peptide fragment that reduced IgE binding and activated T cell is useful for diagnosing, and treating Japanese cedar pollinosis (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include screening for activation of T cells that have been cultured from an individual that is allergic to the allergen as taught by the WO 94/11512 for a method of making modified allergen as taught by Aki *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 94/11512 publication teaches that modified allergen containing T cell epitope with minimal IgE stimulating activity is desirable for diagnosing, and treating Japanese cedar pollinosis (See abstract, page 8, 29-36, in particular).

Claims 37 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aki *et al* (Int Arch Allergy Immunol 103: 357-364, 1994; PTO 892) in view of US Pat No 6,207,646 B1 (March 2001; PTO 892).

The teachings of Aki *et al* have been discussed supra.

The claimed invention as recited in claim 44 differs from the teachings of the reference only in that the method wherein the modified allergen is formulated with an adjuvant such as IFNγ or immune stimulatory sequence oligodeoxynucleotide sequences containing unmethylated CpG motifs which cause brisk activation and skew the immune response to a Th1 type response.

The '646 patent teaches adjuvant such as nucleic acids containing unmethylated CpG motifs is useful for stimulating Th1 immune response such as the production of Th1 cytokines such as IL-12, and IFNγ while suppressing Th2 immune response such as inhibiting the production of IL-4 (See entire document, Abstract, column 6, lines 10-15, in particular). The reference nucleic acids are useful for desensitization therapy to treat or prevent the occurrence of an allergic reaction (See column 6, lines 59-65, claim 3 of '646, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include immune stimulatory sequence oligodeoxynucleotide sequences containing unmethylated CpG motifs for stimulating Th1 immune response such as the production of Th1 cytokines such as IL-12, and IFNγ that suppress Th2 immune response such as inhibiting the production of IL-4 as taught by the '646 patent (See entire document, Abstract, column 6, lines 10-15, in particular) in the method of making any modified allergen as taught by Aki *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '646 patent teaches adjuvant such as nucleic acids containing unmethylated CpG motifs skew the immune response toward Th1 immune response and is useful for desensitization therapy or to treat the occurrence of an allergic reaction (See column 6, lines 59-65, claim 3 of '646, in particular). Aki et al teach making modified allergen by site-directed mutagenesis in combination with IgE binding as measured by colony blot test may indicate which amino acid residues within in each IgE epitope are important for the specificity of allergic sera (See page 363, column 1, in particular).

Claims 37, 48, and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aki *et al* (Int Arch Allergy Immunol 103: 357-364, 1994; PTO 892) in view of Burks *et al* (Eur. J. Biochem. 245: 334-339; 1997, PTO 1449), or Stanley *et al* (Archives of Biochemistry and Biophysics 342(2): 244-253, June 1997; PTO 1449).

The teachings of Aki *et al* have been discussed supra.

The claimed invention as recited in claim 48 differs from the teachings of the reference only in that the method wherein the modified allergen is made from a peanut allergen selected from Ara h1 or Ara h2.

The claimed invention as recited in claim 52 differs from the teachings of the reference only in that the method is a method of making modified food allergen.

The claimed invention as recited in claim 53 differs from the teachings of the reference only in that the method wherein the modified allergen is from crustaceans.

The claimed invention as recited in claim 54 differs from the teachings of the reference only in that the method wherein the modified allergen is shrimp.

Burks *et al* teach a method of making a modified allergen such as peanut allergen Arah1which is less reactive with IgE comprising the steps of identifying one or more IgE binding sites in the reference allergen Ara h1 that bind to serum IgE from individual or pooled serum of individuals who is allergic to peanut allergen (See page 334, Materials and Methods, in particular), modifying the reference peanut allergen by mutating in the center of at least one amino acid in one or more IgE sites by substituting a hydrophobic amino acid (Ala) in the center of one or more of the IgE binding sites with a neutral (Gly) or hydrophilic (Ser) amino acid (See Fig 7, A25G, column 2, paragraph 1, Fig 5, in particular). The reference method screens for IgE binding of modified allergen using serum IgE from an individual or pooled serum from 15 patient with peanut-hypersensitivity (See page 337, column 2, in particular) and selects peptide such as peptides, 1, 3, 4, and 17 which have decrease IgE binding as compared to the control or unmodified wild type allergen (See Fig 6 and 7, in particular). The reference method of making modified-allergen is useful for making hypoallergenic peanut that could blunt allergic reactions in sensitive individual (See page 339, column 1, in particular).

Stanley *et al* teach a method of making a modified food allergen such as peanut allergen Arah2 which is less reactive with IgE comprising the steps of identifying one or more IgE binding sites in the reference allergen Ara h2 that bind to serum IgE from individual or pooled serum of individuals who is allergic to peanut allergen (See entire document, Fig 2, Table III, Abstract, in particular). The reference modified peanut allergen such as Ara h 2 peptides have been mutated

by alanine amino acid substitution and no longer bind IgE when contacted with serum IgE from individual or pooled serum of individuals who are allergic to peanut allergen (See Fig 5, in particular). The reference method of making modified-allergen is useful for allergen immunotherapy that could blunt allergic reactions in sensitive individual (See page 251, column 2, in particular).

The 5,449,669 patent teaches unmodified food allergen from crustacean such as shrimp and IgE binding epitopes (See abstract, in particular). The reference IgE epitopes are useful in diagnosis and/or treatment of allergies.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substituted the house dust mite allergen in the method of making modified allergen as taught by Aki et al for the peanut allergen such as Ara h1 as taught by Burkes et al or the peanut allergen Ara h2 as taught by Stanley *et al* or the shrimp allergen as taught by the '5,449,669 patent for a method of modified any food allergen. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Burks *et al* teach that it is possible to mutate any allergen to a protein so that it no longer binds IgE for making and using hypogenic modified allergen for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph). Stanley *et al* teach that peanuts are a major cause of serious allergic reactions and modified peanut allergen is useful for allergen immunotherapy that could blunt allergic reactions in sensitive individual (See page 251, column 2, in particular). The 5,449,669 patent teaches unmodified food allergen from crustacean such as shrimp and IgE binding epitopes (See abstract, in particular) and IgE epitopes are useful in diagnosis and/or treatment of allergies. Aki et al teach that site-directed mutagenesis in combination with IgE binding as measured by colony blot test may determining which amino acid residues in each epitope are important for the specificity of allergic sera (See page 363, column 1, in particular).

(11) Response to Argument

Claim Rejections - 35 USC § 112 written description

At page 5 of the Brief, Appellant submits that with respect to this rejection, the claims of Group A (claims 37-51 and 57-62) stand or fall together and the claims of Group B (claims 52-54 and 57-62) stand or fall together. By definition, claim groups that cover species of different scope

require a separate written description and/or different levels of written description. Since claim groups A and B cover species of different scope (i.e., methods of making modified protein allergens vs. methods of making modified food allergens), these claim groups must be considered separately and stand or fall separately for purposes of this rejection.

Appellant's arguments have been fully considered but are not found to be persuasive. It is the examiner's position that the written description rejection of claims 37-54 and 57-62 should stand or fall together because of the following reasons:

The methods of making modified protein allergens (genus) in claims 37-51 and 57-62 would include the methods of making modified food allergens (species) in claims 52-54 and 57-62. Species anticipates a genus. Further, claims 57-62 are in both groups.

At page 6 of the Brief, Appellant submits that claims 37-50 were present in substantially the same form as claims 1-13 in the application as originally filed. Claim 51 is a dependent claim that recites limitations found on page 4, lines 10-13 and page 9, line 17 to page 10, line 3 of the specification as filed. Claims 52-54 parallel the language of claim 37 and are of narrower scope (i.e., they are simply limited to food allergens that are described on page 8 and in the Examples). Claims 57-61 recite the limitations found in original claim 14 and the data of Table 6 of the specification as filed (see discussion under Issue 2 below). Claims 62 and 70 recite a limitation found in the section spanning pages 24-25 of the specification as filed. The burden is therefore on the Examiner to overcome the strong presumption of descriptive support with evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. The Examiner has not, and cannot meet this burden; the claimed invention is appropriately described in the specification.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons.

(1) In contrast to appellant's assertion that claims 37-50 were present in substantially the same form as claims 1-13 in the application as originally filed, the original claim 1 recites a method of making a modified allergen which is less reactive with IgE comprising (a) identifying IgE binding sites in an allergen; (b) modifying the allergen by mutating at least one amino acid in an IgE binding site or reacting the allergen with a compound blocking binding to at least one amino acid in an IgE binding site; (c) screening for IgE binding to the modified allergen using serum or antibodies from pooled patient population *and screening for activation of T cells; and (d) selecting the modified allergens which have decreased binding to IgE as compared to the*

unmodified allergen and which activate T cells. Instant claim 37 now recites a method of making a modified allergen which is less reactive with IgE comprising: (a) identifying one or more IgE binding sites in an allergen, the one or more IgE binding sites being ones that are recognized when the allergen is contacted with serum IgE from an individual that is allergic to the allergen; (b) modifying the allergen by mutating at least one amino acid in one or more IgE binding sites; (c) screening for IgE binding to the modified allergen using serum IgE from an individual that is allergic to the allergen; and (d) selecting the modified allergens which have decreased binding to IgE as compared to the unmodified allergen. The method step as recited in Claim 37 now no longer requires the step of screening for activation of T cells; and (d) selecting the modified allergens which have decreased binding to IgE as compared to the unmodified allergen and which activate T cells as required by the original claim 1.

(2) The specification and the claims as originally filed does not define term "substantially" as recited in claims 38-39 which depends from claim 37.

(3) Likewise, the method step as recited in Claim 52 although limited to food allergens still does not require the step of screening for activation of T cells; and (d) selecting the modified allergens which have decreased binding to IgE as compared to the unmodified allergen and which activate T cells as required by the original claim 1.

(4) In contrast to appellant's assertion that claims 57-61 recite the limitations found in claim 14, the original claim 14 recites a modified allergen which is less reactive with IgE comprising at least one IgE binding site present in the allergen modified by at least amino acid change or having at least one amino acid bound by compound so that the site no longer binds IgE, wherein the modified allergen activates T cells, not a method of making modified allergen as claimed.

(5) With regard to the data in Table 6 of the specification, it is noted that Table 6 is limited to modified peanut allergen Ara h3. The scope of claim 27 encompasses a method of a method of making any modified allergen. The scope of claim 52 encompasses a method of making any modified food allergen. The specification and claims as original filed do not have a written support for a method of making any modified allergen or any modified food allergen which is less reactive with IgE comprising: (a) identifying one or more IgE binding sites in an allergen, the one or more IgE binding sites being ones that are recognized when the allergen is contacted with serum IgE from an individual that is allergic to the allergen; (b) modifying the allergen by mutating at least one amino acid such as 1-6, 1-5, 1-4, 1-3, 1-2 amino acids in one or more IgE binding sites; (c) screening for IgE binding to the modified allergen using serum IgE

from an individual that is allergic to the allergen; and (d) selecting the modified allergens which have decreased binding to IgE as compared to the unmodified allergen.

At page 7 of the Brief, Appellant submits the Office issued U.S. Pat. No. 6,048,850 and the decision of Rochester to support appellant's argument that the pending method of making claims are most analogous to methods of identifying in the '850 patent. The specification does contain extensive description of modified protein allergens that can be prepared according to the claimed methods.

Appellant's arguments have been fully considered but are not found to be persuasive. It is well settled that whether similar claims have been allowed to others is immaterial. See In re Giolito, 530 F.2d 397, 188 USPQ 645, 1976. In contrast to appellant's argument that the pending method of making claims are most analogous to methods of identifying in the '850 patent, in order to *make* a modified protein allergen or a food allergen, the particular one or more amino acids, such as 1-6, 1-5, 1-4, 1-3 and 1-2 amino acids in one or more of the IgE binding sites within the full length sequence of which protein allergen has to be identified, let alone the modified protein allergen is based on any protein from any legumes, any milks, any grains, any eggs, any fish, any crustaceans, any mollusks, any insects, any molds, dust, any grasses, any trees, any weeds, any mammals, any birds, and natural latexes, any wheat, any barley, any cow milk, codfish, hazel nut, soybean and shrimp.

At page 8 of the Brief, Appellant submits the Examiner is corrected that the specification does not explicitly set forth the sequences of all possible disruptions to Ara h1, Ara h2 and Ara h3 sites. However, a skilled person, reading the specification, would understand, indeed would explicitly be told, that the presented substitutions were merely exemplary and others would work as well. A skilled artisan would appreciate that the techniques described in the specification would successfully identify all such substitutions. That is, a skilled person would understand that the inventors were in possession of the invention to the full scope of the claims.

Appellant's arguments have been fully considered but are not found to be persuasive. Contrary to appellant's assertion that a skilled person would understand that the inventors were in possession of the invention to the full scope of the claims, a skilled person reading the specification would know that the specification discloses only a method of making modified peanut allergens selected from the group consisting of Ara h1, Ara h2, and Ara h3. With the exception of the specific method of making modified peanut allergen Arh 1, Ara h2 and Ara h3, there is insufficient written description about which particular one or more amino acids within the

full-length sequence of all protein allergen and all food allergen to be modified for the claimed method. There is insufficient written description about the one or more amino acids such as 1-6, 1-5, 1-4, 1-3 and 1-2 amino acids in one or more of the IgE binding sites of all protein allergen such as any protein from legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, trees, weeds, mammals, birds, and natural latexes and all food allergen such as any protein obtained from legumes, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, cow milk, codfish, hazel nut, soybean and shrimp to be modified by the claimed method.

A person skill in the art would also know from reading the specification that the IgE epitope shares no common amino acid sequence motif (see page 4 lines 20-21 of the specification, Table 4-6). The claimed method of making modified allergen with reduced IgE binding is such that determining which one or more amino acids such as 1-6, 1-5, 1-4, 1-3 and 1-2 amino acids in one or more of the IgE binding sites within the full-length protein allergen is empirical by nature. Until the amino acids within the one or more IgE epitope of all protein allergen and all food allergen have been identified, the methods of making any/all modified allergen and any/all food allergen are not adequately described.

At pages 9-10 of the Brief, Appellant submits that the specification explicitly sets out the sequence of several examples of methods of preparing modified peanut allergens. These modified peanut allergens are described as "exemplary" of the inventive principles. For example, the specification recites that "Peanut allergens (Ara h 1, Ara h 2, and Ara h 3) have been used in the examples to demonstrate alteration of IgE binding sites while retaining binding to IgG and activation of T cells" (page 4, lines 15-17). The specification also points to several other common food allergens (see page 8, lines 1-3: "Examples of common food allergens include proteins from peanuts, milk, grains such as wheat and barley, soybeans, eggs, fish, crustaceans, and mollusks."). Moreover, the specification provides references for food allergens whose 1gE epitopes had already been identified (see page 8, lines 4-13). The specification also describes techniques for modifying sequences within IgE sites (see, for example, page 10, lines 3-6 and Examples 2-3), and for identifying those modifications that reduce IgE binding (see, for example, page 4, lines 24-28 and Examples 1-2) in accordance with claim 52. Appellant argues that the rejection for lack of written description should also be removed for the claims of Group A, which stand or fall together for the purposes of this rejection. These claims are broader than those of Group B in that they do not limit the category of protein allergen whose IgE epitopes are modified. Although the claims are broad, there is no failure of written description. The specification makes clear that the

inventive principles are applicable to any allergen (see, for example, page 4, lines 2-14; page 7, line 26 to page 9, line 15; and page 29, lines 18-2%. The specification also specifically lists a variety of relevant allergens (see, for example, page 8, lines 13-16: other allergens include proteins from insects such as flea, tick, mite, fire ant, cockroach, and bee as well as molds, dust, passes, trees, weeds, and proteins from mammals including horses, dogs, cats, etc."). The specification includes extensive discussion of latex allergens, in particular, and provides references reporting IgE epitopes within these allergens (see, for example, page 8, line 19-page 9, line 15). The specification further recites methods of screening for the properties of claims 38-39 and 45 (e.g., see page 4, lines 8-14 and 26-28) and methods for performing the specific modifications of claims 40-43 (e.g., see page 4, lines 17-23 and the Examples). The specification also specifically points to the use of adjuvants having the characteristics recited in claim 44 (e.g., see page 15, lines 19-20) and to the preparation of recombinantly modified allergens as recited in claims 46-47 (e.g., see page 12 and Example 3). Likewise, the specification specifically recites relevant subsets of antigens recited in claims 48-49 (e.g., pages 7-9 and the Examples).

Appellant's arguments have been fully considered but are not found to be persuasive.

The specification does not reasonably provide a **written description** of a method of making *any* modified allergen, *any* modified food allergen and *any* modified peanut allergen as set forth in claims 37-54 and 57-62. The scope of instant claims is drawn to methods of making any modified allergen, or any modified food allergen which is less reactive with IgE.

The specification discloses only a method of making modified peanut allergens selected from the group consisting of Ara h1 (SEQ ID NO: 2), Ara h2 (SEQ ID NO: 4) and Ara h3 (SEQ ID NO: 6) depicted in Figs 1-3. The amino acids that are critical for IgE binding of Ara h1, Ara h2 and Ara h3 are listed in Table 4, 5 and 6, respectively (See page 26-27). The specification also discloses that a single amino acid substitution by changing amino acid to alanine or glycine within the IgE binding epitope of Ara h1 (See page 24, line 16-18) leads to a reduced IgE binding whereas substituting alanine for arginine of Ara h1 lead to an increased IgE binding (See page 24, line 26-28). Likewise, a single amino acid within the IgE binding epitope of Ara h2 (Table 5) and Ara h3 (Table 6) would decrease IgE binding. The modified Ara h2 not only binds less serum IgE than the wild type but also binds similar amounts of IgG (See page 28, line 14-15; Fig. 4B) using serum from patients sensitive to peanut allergens. The specification further discloses that the modified Ara h2 retains the ability to stimulate T cell proliferation as measured by tritiated

thymidine incorporation and the modified Ara h2 elicits a smaller wheal and flare in skin prick tests of a peanut sensitive individual (page 29).

With the exception of the specific method of making modified peanut allergen Arh 1, Ara h2 and Ara h3, there is insufficient written description about which particular one or more amino acids within the full-length sequence of all protein allergen and all food allergen to be modified for the claimed method. There is insufficient written description about the one or more amino acids such as 1-6, 1-5, 1-4, 1-3 and 1-2 amino acids in one or more of the IgE binding sites of all protein allergen such as any protein from legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, trees, weeds, mammals, birds, and natural latexes and all food allergen such as any protein obtained from legumes, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, cow milk, codfish, hazel nut, soybean and shrimp to be modified by the claimed method. Until the amino acids within the one or more IgE epitope of all protein allergen and all food allergen have been identified, the methods of making the modified allergen and food allergen are not adequately described.

Further, the specification disclosed only a method of making three species of modified food allergens from only peanut (a member of the legumes family), given the lack of a written description of any additional species of allergen from other protein allergen and food allergen as encompassed by the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).* Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

At page 11 of the Brief, Appellant argues that significant sequence information is provided in this case. The pending claims related to a method, not to the nucleic acids or proteins themselves.

Appellant's arguments have been fully considered but are not found to be persuasive.

As discussed supra, the pending claims are drawn to a method of making, not a method of screening. In order to make any modified allergen, the amino acid sequence or the corresponding nucleotide sequence of the modified allergen is required.

Claim Rejections - 35 USC § 112 new matter

At page 11 second paragraph of the Brief, appellant states that these claims are fully supported by the specification and claims as originally filed. In particular, original claim 1 recites a step of " modifying the allergen by mutating at least one amino acid in an IgE binding site [...]. Original claim 1 therefore makes it perfectly clear that the present invention encompasses methods that include a step of modifying more than one amino acid residue within an IgE epitope. The specification as filed further teaches IgE epitopes that include 1, 2, 3, 4, 5 or 6 amino acid residues that, when altered, lead to a reduction in IgE binding (e.g., see epitopes 5, 7, 8, 9, 18 in Table 4 and epitope 4 in Table 6 (page 26 and page 27, respectively). The specification and claims ms originally filed therefore clearly support the language of pending claims 57-61.

Appellant's arguments have been fully considered but are not found to be persuasive for the following reasons.

(1) It is noted that epitope 4 in Table 6 is limited to modified peanut allergen Ara h3 while epitopes 1-6 in Table 26 is limited to peanut allergen Ara h1, not any allergen or any food allergen.

(2) claims 57-62 recite the methods of making any modified allergen or any modified food allergen which is less reactive with IgE comprising: (a) identifying one or more IgE binding sites in an allergen, the one or more IgE binding sites being ones that are recognized when the allergen is contacted with serum IgE from an individual that is allergic to the allergen; (b) modifying the allergen by mutating at least one amino acid in one or more IgE binding sites; (c) screening for IgE binding to the modified allergen using serum IgE from an individual that is allergic to the allergen; and (d) selecting the modified allergens which have decreased binding to IgE as compared to the unmodified allergen wherein the step of modifying includes modifying at least 1-6, 1-5, 1-4,1-3 or 1-2 amino acids in at least one IgE epitope of any allergen or any food allergen.

(3) Claims 57-62 do not recite a method of making *peanut allergen* which is less reactive with IgE wherein the step of modifying includes modifying at least 1-6, 1-5, 1-4,1-3 or 1-2 amino acids in at least one IgE epitope. The original claim 1 recites a method of making a modified allergen which is less reactive with IgE comprising (a) identifying IgE binding sites in an allergen; (b) modifying the allergen by mutating at least one amino acid in an IgE binding site or reacting the allergen with a compound blocking binding to at least one amino acid in an IgE binding site; (c) screening for IgE binding to the modified allergen using serum or antibodies from pooled patient population *and screening for activation of T cells; and (d) selecting the modified allergens*

which have decreased binding to IgE as compared to the unmodified allergen and which activate T cells.

(4) The specification and claims as original filed do not have a written support for a method of making any modified allergen or any modified food allergen which is less reactive with IgE comprising: (a) identifying one or more IgE binding sites in an allergen, the one or more IgE binding sites being ones that are recognized when the allergen is contacted with serum IgE from an individual that is allergic to the allergen; (b) modifying the allergen by mutating at least one amino acid such as 1-6, 1-5, 1-4, 1-3, 1-2 amino acids in one or more IgE binding sites; (c) screening for IgE binding to the modified allergen using serum IgE from an individual that is allergic to the allergen; and (d) selecting the modified allergens which have decreased binding to IgE as compared to the unmodified allergen as now claim.

Claim Rejections - 35 USC § 112 second paragraph

At paragraph bridging page 11 and 12 of the Brief, Appellant notes that the term "substantially" is not used in claim 37. Thus the rejection presumably only applies to claims 38-39. With respect to this rejection claim 37 stands or falls alone and claims 38-39 stand or fall together. Appellant respectfully disagrees with this rejection. The courts have clearly stated that expressions such as "substantially" may be used in patent claims when warranted by the nature of invention, in order to accommodate the minor variations that may be appropriate to secure the invention. Verve LLC v. Crane Cams, 311 F.3d 1 116 (Fed. Cir. 2002). The nature of the presently claimed invention is such that the selection of modified allergens that exhibit minor variations in T-cell activation (claim 38) or IgG binding (claim 39) as compared to an unmodified allergen could be made without losing the benefit of the present invention. One skilled in the art, upon reading the present specification, would readily recognize such trivial variations.

Appellant's arguments have been fully considered but are not found to be persuasive. Appellant is correct to presume that this rejection is applied to claims 38-39 since claim 37 does not recite "substantially". However, claims 38-39 depend from claim 37. Therefore, claim 37 is included in this rejection. Although the term "substantially" may be used in the claims if the specification clearly defines what is meant by "substantially", the instant specification does not define what is meant by "substantially the same". Therefore, modified allergens that exhibit 50% difference in T-cell activation (claim 38) or IgG binding (claim 39) would still be substantially the same. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

Claim Rejections - 35 USC § 102(b)

Claims 37, 39-43, 46-47, 49-51, and 57-62 are rejected under 35 U.S.C. 102(b) as being anticipated by Aki *et al* (Int Arch Allergy Immunol 103: 357-364, 1994; PTO 892).

At pages 12-13 of the Brief, Appellant argues that Aki et al does not teach at least steps (b)-(d) of claim 37. The Examiner suggests that Aki et al. teaches a method that includes a step of modifying an allergen by "mutating at least one amino acid in the center of IgE binding sites" (see page 4 of Office Action mailed October 3, 2003). In this context, the Examiner points to pages 360-361 of Aki et al. Appellant disagrees and respectfully submits that Aki et al. never teaches the modification of a natural allergen as claimed herein. Instead, Aki et al. teaches the preparation and modification of a wholly artificial β-galactosidase-Magl-Ez fusion protein (e.g., see p. 359, column 2, last sentence and pp. 360-361). Magl-E2 is an isolated IgE epitope that corresponds to amino acids 104-115 of the dust mite allergen Mag 1. β-galactosidase is a large enzyme (1024 amino acids and 1 16 kDa) that catalyzes the hydrolysis of terminal, non-reducing β-d-galactose residues in beta-galactosides. Thus, this artificial fusion protein is not a natural allergen that falls within the scope of claim 37. Certainly its sequence and physical properties bear no resemblance whatsoever to those of the natural 39 kDa dust mite allergen Mag 1 taught by Aki et al. nor is the fusion protein a "portion of a natural allergen that includes all of the IgE binding sites of the natural allergen" as defined in claim 43.

Appellant's arguments have been fully considered but are not found to be persuasive. It is noted that Claim 37 does not recite identifying one or more IgE binding sites in a *natural* allergen. Contrary to appellant's assertion that Aki et al does not teach at least steps (b)-(d) of claim 37, Aki et al teach a method of making modified allergen such as allergen Mag1E2, Magl-E2 from house dust mite which is less reactive with IgE. The reference method comprises identifying one or more IgE binding sites in an allergen such as dust mite (see page 359, Fig 1B WT, clones 301-308, 501-505, R02, col. b and c, in particular) by contacting the full length allergen and overlapping fragment thereof (see Fig 1 B, clones 301-305, amino acid ranging from 1-267 to 1-152, c, in particular) with serum IgE from an individual (see Fig 1 c, in particular) or pooled serum from 8 mite-allergic patients (See page 359, Fig 1 b, page 360, column 1, in particular). Once the IgE epitopes such as Magl-E2 corresponding to amino acids 56 to 70 of the full length dust mite allergen has been identified, the dodecapeptide was synthesized by the Fmoc method (see page 359, col. 1, peptide synthesis, page 360, col. 1, last paragraph, in particular) and the allergen was modified by mutating at least one amino acid in the center of IgE binding sites by site-directed mutagenesis such as substituting hydrophobic amino acid such as Ala, Leu, and

Isolucine for neutral amino acid such as glycine or hydrophilic amino acid such as arginine (See page 361, column 1, page 360, column 1, last full paragraph, Fig 4, in particular). As pointed out by Aki et al, the pending method steps are not novel. Reactivities of synthetic overlapping peptides, spanning the entire sequence of allergen Der pII to IgE in mite allergic sera suggested that a peptide comprising residue 65-78 was a sequential IgE biding epitope (see page 357, col. 2 in particular). In fact, the specification on page 17 discloses that individual peptides were synthesized using 9-Fmoc. The specification discloses overlapping peptides of peanut allergen is synthesized, screened with pooled serum IgE antibody from peanut sensitive patients (see page 24, line 1-5, in particular). Once the IgE epitope has been identified, the peptide is synthesized and mutated by amino acid substitution such as Q at position 143 change to A (see page 24, lines 15-16 of specification, in particular). It is absurd to say the least that Aki et al does teach the claimed invention.

In response to appellant's argument that Mag 1. β-galactosidase is not a natural allergen, the β-galactosidase in β-galactosidase-Magl-Ez fusion protein is merely a tool for purifying the recombinant allergen, very much like the histidine tag fused to the recombinant Ara h2 allowing the recombinant protein to be purified as disclosed on page 19 of the specification. The β-galactosidase is irrelevant since it does not interfere with the binding of IgE to the allergen or modified allergen in the method step.

In contrast to appellant's assertion that the allergen sequence and physical properties bear no resemblance whatsoever to those of the natural 39 kDa dust mite allergen Mag 1 taught by Aki et al, Aki et al teach various overlapping peptides, spanning the entire sequence of the reference allergen, as well as the full length (WT) sequence of the allergen were made recombinantly and use for IgE binding screening (see Figure 1B, clone and amino acid range, in particular). Once the IgE epitopes such as Mag1-E2 corresponding to amino acids 56 to 70 of the full length dust mite allergen has been identified, the modified allergen dodecapeptide was synthesized by the Fmoc method (see page 359, col. 1, peptide synthesis, page 360, col. 1, last paragraph, in particular) and the allergen was modified by mutating at least one amino acid in the center of IgE binding sites by site-directed mutagenesis such as substituting hydrophobic amino acid such as Ala, Leu, and Isolucine for neutral amino acid such as glycine or hydrophilic amino acid such as arginine (See page 361, column 1, page 360, column 1, last full paragraph, Fig 4, in particular).

Claim Rejections - 35 USC § 102(a))

Claims 37, 40-43, 48-53, and 57-62 are rejected under 35 U.S.C. 102(a) as being anticipated by Burks *et al* (Eur. J. Biochem. 245: 334-339; 1997, PTO 1449).

At paragraph bridging page 14 and 15 of the Brief, appellant argues that this rejection should be removed quite simply because Burks et al is not prior art. The relevant teachings of Burks et al. were included near verbatim in U.S. Serial No. 08/717,933 filed September 23, 1996 (see pp. 133-155 and the Figures referred to therein). The 1996 filing was made by Appellant in part to protect the teachings of Burks et al.

Appellant's arguments have been fully considered but are not found to be persuasive.

In contrast to appellant's assertion that that the teachings of Burks et al cannot be used as prior art under 35 U.S.C. §102(a), the filing date of the instant claims is deemed to be the filing date of USSN 60/073,283 filed January 31, 1998 because of the following reasons:

(1) USSN 08/717,933 (filed September 1996) is drawn to a method of making modified peanut antigen Ara h1 (see Table 22 on page 153 of 08/717,933), and peanut peptides of Ara h2 (see Table 26 on page 171 of 08/717,933), monoclonal antibody specific to a selected peanut allergen, hybridoma and immunoassay to be used for determining the concentration of a specific allergen (Ara h I) (See summary of invention, pages 6-12, claims of 08/717,933, in particular).

(2) The USSN 08/717,933 does not have a written support for the claimed limitations of a method of making any modified allergen which is less reactive with IgE comprising: (a) identifying one or more IgE binding sites in an allergen, the one or more IgE binding sites being ones that are recognized when the allergen is contacted with serum IgE from an individual that is allergic to the allergen; (b) modifying the allergen by mutating at least one amino acid in one or more IgE binding sites; (c) screening for IgE binding to the modified allergen using serum IgE from an individual that is allergic to the allergen; and (d) selecting the modified allergens which have decreased binding to IgE as compared to the unmodified allergen (claim 37), and any modified food allergen (claim 52) as now claim, much less the dependent claims therefrom.

(3) The USSN 08/717,933 does not have a written support for the claimed limitations of a method of making modified peanut allergen Ara h3 (claim 48).

(4) The USSN 08/717,933 does not have a written support for a method of making any modified allergen or any modified food allergen which is less reactive with IgE comprising: (a) identifying one or more IgE binding sites in an allergen, the one or more IgE binding sites being ones that are recognized when the allergen is contacted with serum IgE from an individual that is allergic to the allergen; (b) modifying the allergen by mutating at least one amino acid in one or

more IgE binding sites; (c) screening for IgE binding to the modified allergen using serum IgE from an individual that is allergic to the allergen; and (d) selecting the modified allergens which have decreased binding to IgE as compared to the unmodified allergen wherein step of modifying includes modifying at least *1-6, 1-5, 1-4, 1-3, or 1-2* amino acids in at least one IgE epitope of the allergen (claims 57-61).

Other than the method of making the specific modified allergen from peanut Ara h1 and Ara h2, the USSN 08/717,933 does not have the support for the method of making any modified allergen and any food allergen (claims 37 and 52), peanut allergen (claim 48) and dependent claims thereof. Therefore, claims 37, 40-43, 48-53, and 57-62 can only have the benefit under U.S.C. 119 (e) of filing date of provisional application 60/073,283 filed January 31, 1998. Burks et al. is prior art references under 35 U.S.C. §102(a) because the reference is published April 1997.

Claims 37, 40-43, 48-53, and 55-62 are rejected under 35 U.S.C. 102(a) as being anticipated by Stanley *et al* (Archives of Biochemistry and Biophysics 342(2): 244-253, June 1997; PTO 1449).

At page 15 of the Brief, appellant argues that this rejection should be removed quite simply because Stanley et al is not prior art. The relevant teachings of Burks et al. were included near verbatim in U.S. Serial No. 08/717,933 filed September 23, 1996 (see pp. 156-174 and 176-180). The 1996 filing was made by Appellant in part to protect the teachings of Stanley et al.

Appellant's arguments have been fully considered but are not found to be persuasive.

In contrast to appellant's assertion that that the teachings of Stanley et al cannot be used as prior art under 35 U.S.C. §102(a), the filing date of the instant claims is deemed to be the filing date of USSN 60/073,283 filed January 31, 1998 because of the following reasons:

(1) USSN 08/717,933 (filed September 1996) is drawn to a method of making modified peanut antigen Ara h1 (see Table 22 on page 153 of 08/717,933), and peanut peptides of Ara h2 (see Table 26 on page 171 of 08/717,933), monoclonal antibody specific to a selected peanut allergen, hybridoma and immunoassay to be used for determining the concentration of a specific allergen (Ara h I) (See summary of invention, pages 6-12, claims of 08/717,933, in particular).

(2) The USSN 08/717,933 does not have a written support for the claimed limitations of a method of making any modified allergen which is less reactive with IgE comprising: (a) identifying one or more IgE binding sites in an allergen, the one or more IgE binding sites being ones that are recognized when the allergen is contacted with serum IgE from an individual that is

allergic to the allergen; (b) modifying the allergen by mutating at least one amino acid in one or more IgE binding sites; (c) screening for IgE binding to the modified allergen using serum IgE from an individual that is allergic to the allergen; and (d) selecting the modified allergens which have decreased binding to IgE as compared to the unmodified allergen (claim 37), and any modified food allergen (claim 52) as now claim, much less the dependent claims therefrom.

(3) The USSN 08/717,933 does not have a written support for the claimed limitations of a method of making modified peanut allergen Ara h3 (claim 48).

(4) The USSN 08/717,933 does not have a written support for a method of making any modified allergen or any modified food allergen which is less reactive with IgE comprising: (a) identifying one or more IgE binding sites in an allergen, the one or more IgE binding sites being ones that are recognized when the allergen is contacted with serum IgE from an individual that is allergic to the allergen; (b) modifying the allergen by mutating at least one amino acid in one or more IgE binding sites; (c) screening for IgE binding to the modified allergen using serum IgE from an individual that is allergic to the allergen; and (d) selecting the modified allergens which have decreased binding to IgE as compared to the unmodified allergen wherein step of modifying includes modifying at least *1-6, 1-5, 1-4, 1-3, or 1-2* amino acids in at least one IgE epitope of the allergen (claims 57-61).

Other than the method of making the specific modified allergen from peanut Ara h1 and Ara h2, the USSN 08/717,933 does not have the support for the method of making any modified allergen and any food allergen (claims 37 and 52), peanut allergen (claim 48) and dependent claims thereof. Therefore, claims 37, 40-43, 48-53, and 57-62 can only have the benefit under U.S.C. 119 (e) of filing date of provisional application 60/073,283 filed January 31, 1998. Stanley et al. is prior art references under 35 U.S.C. §102(a) because the reference is published June 1997.

Claim Rejections - 35 USC § 103(a)

Claims 37-38 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aki *et al* (Int Arch Allergy Immunol 103: 357-364, 1994; PTO 892) in view of WO 94/11512 publication (May 1994, PTO 892).

At last paragraph on page 15 of the Brief, Appellant submits that the teachings of Aki et al. and its deficiencies with regards to claim 37 have been discussed supra. WO 94/1 1512 is a secondary reference that is cited solely as teaching limitations that are found in dependent claims 38 and 49, namely a step of screening for activation of T-cells and the use of an allergen from

trees. The Examiner points to no teaching or suggestion in WO 94/11512 that could overcome the aforementioned deficiencies of Aki et al.

Appellant's arguments have been fully considered but are not found to be persuasive. As discussed supra, Claim 37 does not recite identifying one or more IgE binding sites in a *natural* allergen. Contrary to appellant's assertion that Aki et al does not teach at least steps (b)-(d) of claim 37, Aki et al teach a method of making modified allergen such as allergen Mag1E2, Mag1-E2 from house dust mite which is less reactive with IgE wherein the method comprises identifying one or more IgE binding sites in an allergen such as dust mite (see page 359, Fig 1B WT, clones 301-308, 501-505, R02, col. b and c, in particular) by contacting the full length allergen and overlapping fragment thereof spanning the entire sequence of the reference allergen (see Fig 1 B, clones 301-305, amino acid ranging from 1-267 to 1-152, c, in particular) with serum IgE from an individual (see Fig 1 c, in particular) or pooled serum from 8 mite-allergic patients (See page 359, Fig 1 b, page 360, column 1, in particular). Once the IgE epitopes such as Mag1-E2 corresponding to amino acids 56 to 70 of the full length dust mite allergen has been identified, the dodecapeptide was synthesized by the Fmoc method (see page 359, col. 1, peptide synthesis, page 360, col. 1, last paragraph, in particular) and the allergen was modified by mutating at least one amino acid in the center of IgE binding sites by site-directed mutagenesis such as substituting hydrophobic amino acid such as Ala, Leu, and Isolucine for neutral amino acid such as glycine or hydrophilic amino acid such as arginine (See page 361, column 1, page 360, column 1, last full paragraph, in particular). Aki et al teach the method step is not novel as reactivities of synthetic overlapping peptides, spanning the entire sequence of Der pII to IgE in mite allergic sera suggested that a peptide comprising residue 65-78 was a sequential IgE biding epitope (see page 357, col. 2 in particular). In fact, the specification on page 17 discloses that individual peptides were synthesized using 9-Fmoc. The specification discloses overlapping peptides of peanut allergen is synthesized, screened with pooled serum IgE antibody from peanut sensitive patients (see page 24, line 1-5, in particular). Once the IgE epitope has been identified, the peptide is synthesized and mutated by amino acid substitution such as Q at position 143 change to A (see page 24, lines 15-16, in particular). The reference modified allergens have decrease IgE binding while IgG binding is substantially the same as the unmodified allergen (see page 361, column 1, third paragraph, Fig 4, in particular). The reference modified allergen is a portion of the allergen which corresponds to Ser56 to Lys70 or Asp104 to Ala 115 of the unmodified dust allergen (See page 360, column 1, third paragraph, in particular). The reference modified allergen can also be made in a recombinant host such as bacteria as fusion protein to β-

galactosidase (See page 358, Materials and Methods, in particular). It is absurd to say the least that Aki et al does teach the claimed invention.

In response to appellant's argument that Mag-1- β-galactosidase is not a natural allergen, the β-galactosidase in β-galactosidase-Magl-Ez fusion protein is merely a tool for purifying the recombinant allergen, very much like the histidine tag fused to the recombinant Ara h2 allowing the recombinant protein to be purified as disclosed on page 19 of the specification. The β-galactosidase is irrelevant since it does not interfere with the binding of IgE to the allergen or modified allergen in the method step.

In contrast to appellant's assertion that the allergen sequence and physical properties bear no resemblance whatsoever to those of the natural 39 kDa dust mite allergen Mag 1 taught by Aki et al, Aki et al teach various overlapping peptides, spanning the entire sequence of the reference allergen, as well as the full length (WT) sequence of the allergen were made recombinantly and use for IgE binding screening (see Figure 1B, clone and amino acid range, in particular). Once the IgE epitopes such as Magl-E2 corresponding to amino acids 56 to 70 of the full length dust mite allergen has been identified, the modified allergen dodecapeptide was synthesized by the Fmoc method (see page 359, col. 1, peptide synthesis, page 360, col. 1, last paragraph, in particular) and the allergen was modified by mutating at least one amino acid in the center of IgE binding sites by site-directed mutagenesis such as substituting hydrophobic amino acid such as Ala, Leu, and Isolucine for neutral amino acid such as glycine or hydrophilic amino acid such as arginine (See page 361, column 1, page 360, column 1, last full paragraph, Fig 4, in particular).

Claims 37 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aki *et al* (Int Arch Allergy Immunol 103: 357-364, 1994; PTO 892) in view of US Pat No 6,207,646 B1 (March 2001; PTO 892).

At first paragraph on page 16 of the Brief, Appellant submits that the teachings of Aki et al. and its deficiencies with regards to claim 37 have been discussed supra. U.S. Pat. 6,207,646 is a secondary reference that is cited solely as teaching limitations that are found in dependent claim 44, namely a step of formulating the modified allergen with a specific adjuvant. The Examiner points to no teaching or suggestion in U.S. Pat. 6,207,646 that could overcome the aforementioned deficiencies of Aki et al.

Appellant's arguments have been fully considered but are not found to be persuasive.

The rebuttal of the Examiner has been discussed supra and is incorporated here by reference.

Claims 37, 48, and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aki *et al* (Int Arch Allergy Immunol 103: 357-364, 1994; PTO 892) in view of Burks *et al* (Eur. J. Biochem. 245: 334-339; 1997, PTO 1449), or Stanley *et al* (Archives of Biochemistry and Biophysics 342(2): 244-253, June 1997; PTO 1449) or US Pat No. 5,449,669 (Sept 1995, PTO 892).

At second paragraph on page 16 of the Brief, Appellant submits that the teachings of Aki et al. and its lacking have been discussed supra. As discussed supra, Burks et al. and Stanley et al. are not available as prior art under 35 U.S.C. § 103(a). U.S. Pat. No. 5,449,669 is cited solely as teaching an unmodified protein allergen, namely shrimp tropomyosin, and its two IgE binding epitopes. The Examiner points to no teaching or suggestion in U.S. Pat. 5,449,669 that could overcome the deficiencies of Aki et al.

Appellant's arguments have been fully considered but are not found to be persuasive. The rebuttal of the Examiner has been discussed supra and is incorporated here by reference. In contrast to appellant's argument that Burks et al. and Stanley et al. are not available as prior art, the filing date of the instant claims 37, 48 and 52-54 is deemed to be the filing date of USSN 60/073,283 filed January 31, 1998 because of the following reasons:

(1) USSN 08/717,933 (filed September 1996) is drawn to a method of making modified peanut antigen Ara h1 (see Table 22 on page 153 of 08/717,933), and peanut peptides of Ara h2 (see Table 26 on page 171 of 08/717,933), monoclonal antibody specific to a selected peanut allergen, hybridoma and immunoassay to be used for determining the concentration of a specific allergen (Ara h I) (See summary of invention, pages 6-12, claims of 08/717,933, in particular).

(2) The USSN 08/717,933 does not have a written support for the claimed limitations of a method of making any modified allergen which is less reactive with IgE comprising: (a) identifying one or more IgE binding sites in an allergen, the one or more IgE binding sites being ones that are recognized when the allergen is contacted with serum IgE from an individual that is allergic to the allergen; (b) modifying the allergen by mutating at least one amino acid in one or more IgE binding sites; (c) screening for IgE binding to the modified allergen using serum IgE from an individual that is allergic to the allergen; and (d) selecting the modified allergens which have decreased binding to IgE as compared to the unmodified allergen (claim 37), and any modified food allergen (claim 52) as now claim, much less the dependent claims therefrom.

(3) The USSN 08/717,933 does not have a written support for the claimed limitations of a method of making modified peanut allergen Ara h3 (claim 48).

Other than the method of making the specific modified allergen from peanut Ara h1 and Ara h2, the USSN 08/717,933 does not have the support for the method of making any modified allergen and (claims 37), any peanut allergen such as Ara h3 (claim 48) and dependent claims thereof. Therefore, claims 37, 48 and dependent claims 42-54 can only have the benefit under U.S.C. 119 (e) of filing date of provisional application 60/073,283 filed January 31, 1998. Both Burks et al. and Stanley et al reference are prior art references under 35 U.S.C. §102(a) because the references are published April 1997 and June 1997, respectively. Therefore, both Burks et al and Stanley et al references are available as prior art under 103(a).

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Phuong N Huynh
February 4, 2005

Conferees

Christina Chan
SPE, Art unit 1644

James Housel
SPE, Art unit 1648